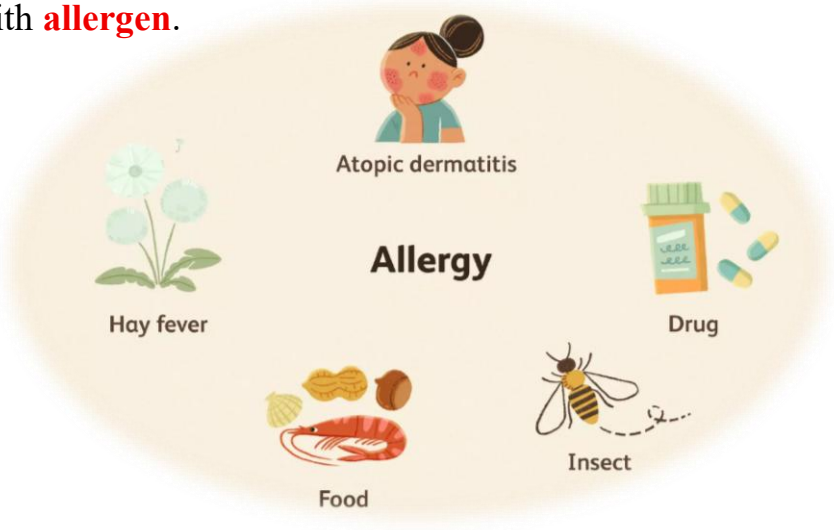
Hypersensitivity (Allergy)

☞ **Definition** of **allergy**: Allergy or Hypersensitivity is an **altered reactivity** of the tissue of certain individual, caused by exposure to an agent (**allergen**) that is innocuous to other persons.

Or

Altered reactivity on second contact with **allergen**.

☞ **Definition** of **Allergen**: is an **antigen** that can elicit **allergic** symptoms.



In simple words **allergy** is where your body **reacts** to something that's normally harmless like pollen, dust or animal fur.

➢ **Allergic response** to an **allergen** may occur <u>secondary to</u>: (**routes** of exposure to allergens):

- Inhalation.
- Injection.
- Ingestion.
- Contact with skin.

Classification *of* ***hypersensitivity reactions*** *on the basis of* ***mechanisms*** *involved in their production:*

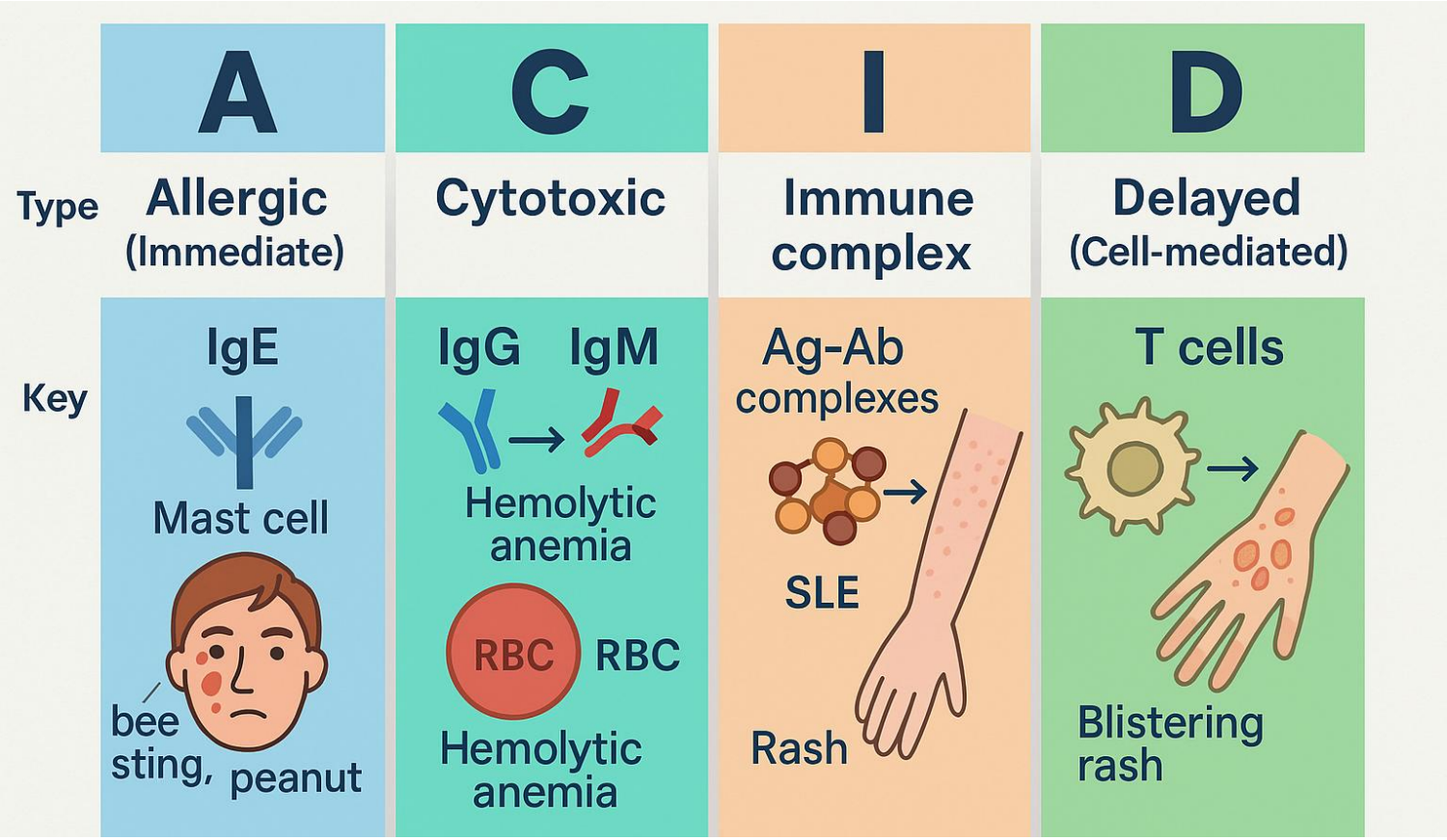
Gell & Coombs classification (1970).

1- **Immediate** allergic reactions include **types I, II & III**:

- ✓ ***Definition***: Immediate hypersensitivity is an allergic reaction that occurs rapidly after exposure to an allergen.
- ✓ ***Symptoms***: May include rash, hives, difficulty breathing, and nausea.

2- **Delayed** allergic reaction include **type IV**:

- ✓ ***Definition***: Delayed-type hypersensitivity is a type of immune response involving T-cell activation after antigen exposure.
- ✓ ***Symptoms***: It causes redness, swelling and **tissue damage** at the site, appearing at least **12-24 hours** after exposure and up to **48-72 hours** after exposure.



Drugs *used to* ***treat*** ***hypersensitivity****:*

1- **Adrenaline** (**epinephrine**): **First** line of treatment in **emergency** situations as anaphylactic shock, bronchial asthma & angioedema.

⇨ **Adrenaline** produces:

- ☑ **Bronchodilatation**.
- ☑ **Vasoconstriction**.
- ☑ Decreases capillary permeability, thus reduces edema.

⇨ **Adrenaline** acts within few minutes (**fast onset**) leading to increase in blood pressure and stimulation of heart muscle.

↪ Such actions are life-saving in particular with anaphylactic shock.

⇨ **Dose**: **0.5 ml** (**1/1000**) **conc**., injected **I.M.** or **S.C.**

- Re-administered after **5 minutes** if there is no improvement with **maximum** dose of **1.5 ml**.
- NB. For young children, the dose will be **reduced** to **0.1 - 0.3 mL** of **adrenaline**.
- Never to be given **I.V.** to avoid ventricular fibrillation.

2- **Corticosteroids**:

⇨ Effects / Uses / **Indications**:

- ☑ Anti-inflammatory.
- ☑ Immunosuppressant.
- ☑ Anti-lymphocytic cytotoxic in oncology.
- ☑ In the management of allergic diseases.

⇨ In allergic processes, **corticosteroids** can:

- **Suppress** the production and effects of humoral factors involved in the inflammatory response.
- **Inhibit** the migration of leukocytes to sites of inflammation.
- **Interfere** with the function of endothelial cells, granulocytes, mast cells, and fibroblasts.

3- **Antihistaminics**:

⇨ **Effects**:

- ☑ They **antagonize** one mediator only (**histamine**).
- ☑ They are **slowly acting** drugs.
- ☑ They **restore** the **vasomotor tone** *without* producing potential vasoconstriction.
- ☑ They have **no value** in emergency.

⇨ **Examples** of antihistaminic drugs:

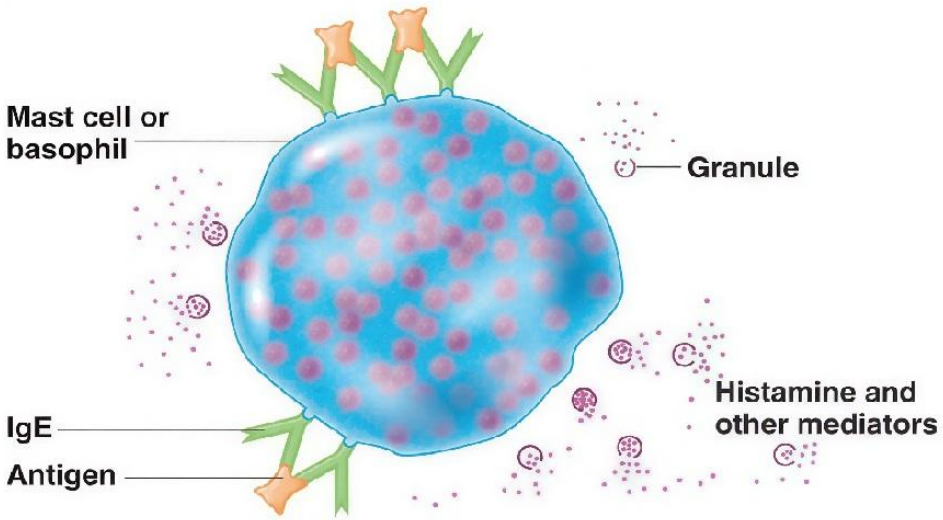
- ✓ Promethazine (phenergan).
- ✓ Mepyramine (Anthisan cream).
- ✓ Tripelennamine (Pyribenzamine).
- ✓ Diphenhydramine (Benadryl).
- ✓ Chlorpheniramine Cetirizine (Zyrtec).
- ✓ Loratadine (Claritin).

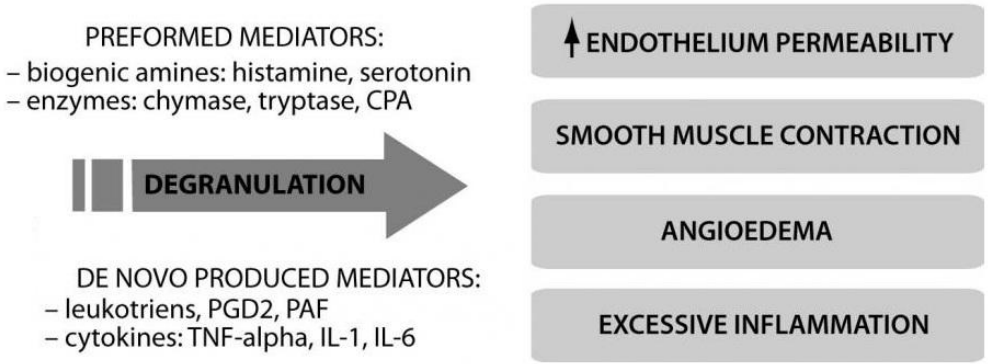
Type-I Hypersensitivity Reaction

- Also known as **immediate** hypersensitivity maybe caused by **genetics** (atopy).
- **Atopy**: Subset of allergic reaction, characterized by hereditary tendency to develop **IgE**-mediated illness in response to **allergen**.
- **N.B.** Normal individuals who are non-allergic have low level of circulating **IgE** (0.004%).

Mechanism (Pathophysiology) of anaphylaxis:

- ✓ **IgE antibodies**, produced in response to an **antigen**, coat **mast cells** and **basophils**, when an **antigen bridges** the gap between two adjacent antibody molecules of the same specificity, the cells under-go degranulation, releases histamine & other mediators.





- **Examples** of Type-l allergic reactions:

(a) **Generalized** anaphylaxis: Anaphylactic shock.

(b) **Localized** anaphylaxis:

- Bronchial asthma.
- Angioedema.
- Hay fever.
- Urticaria.

1) Anaphylactic shock:

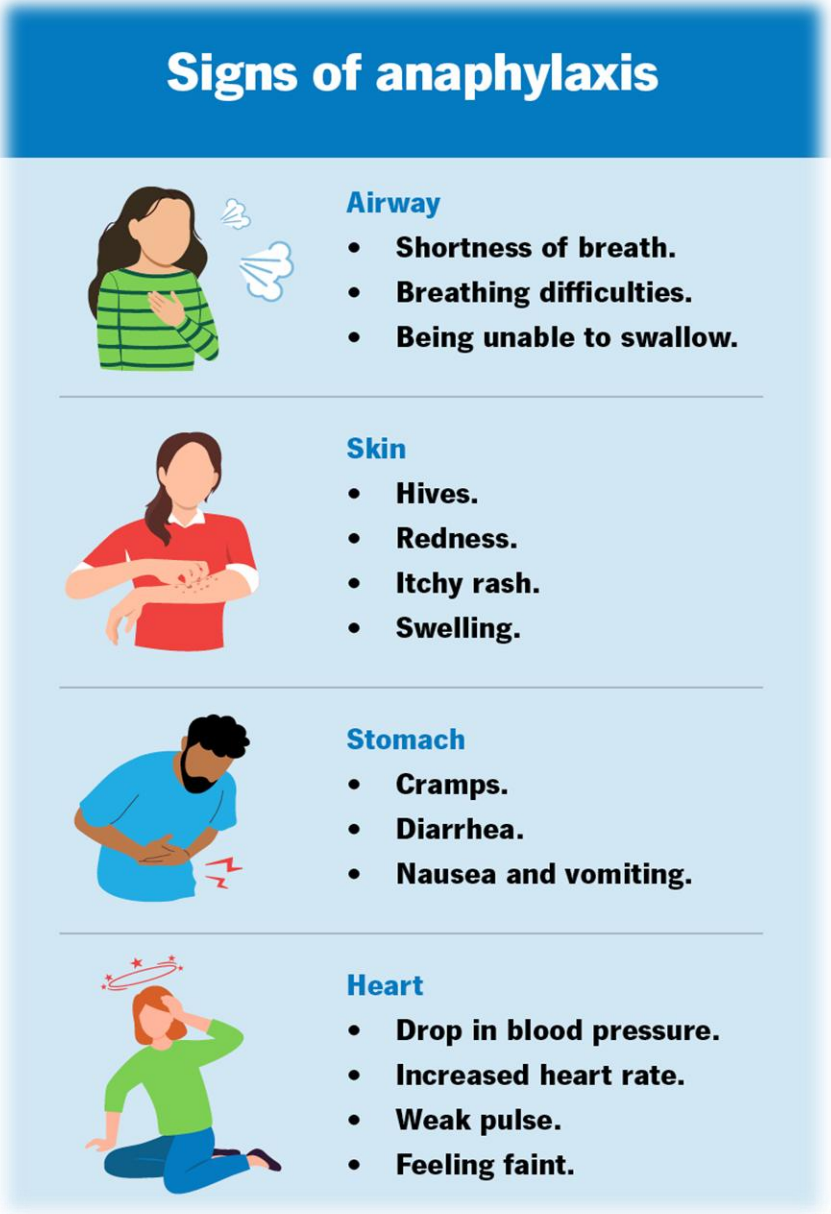
- **Definition**: Most dramatic & dangerous reaction that may follow administration of foreign protein or drug in sensitized individuals.
- The reaction is **acute** with simultaneous **involvement** of **CVS**, **RS**, **GIT** & **skin**.
- The reaction usually starts within **30 minutes** (may be **30 second**) after injection of a drug (allergen).
- The **quicker** the onset, the **more severe** the reaction.

Clinical Features of anaphylactic shock:

1) **Earlier** starts as:
   - Paraesthesia and edema of the face.
   - Coldness of hands and feet.
   - Wheeze due to bronchospasm.
   - Rapid severe fall of blood pressure.
   - Pallor and sweating.
   - Fast thready pulse.
   - Loss of consciousness.

In **severe** cases

2) **Later**:
   - The patient is pulseless.
   - Cyanosis from inadequate oxygenation.
   - Death may occur within five minutes.



Management / **Treatment** of **anaphylactic shock**:

1- Lay the patient flat with legs raised (**Trendelenburg position**):

↬ *This position improves venous return from the body peripheral regions to the heart and increases blood flow to the brain.*

2- **Adrenaline**: Inject **I.M**. or **S.C.**:

- ✓ **Dose: 0.5 ml (1/1000) conc**., re-administered after **5 minutes** if there is no improvement with **maximum** dose of **1.5 ml**.
- ✓ NB. For young children, the dose will be **reduced** to **0.1 - 0.3 mL** of **adrenaline**.
- ✓ Never to be given **I.V.** to avoid ventricular fibrillation.
- ✓ You can also use epinephrine autoinjectors (**EpiPen**) in the thigh **muscle** if you have it.

3- **Oxygen** & **monitoring** of **vital signs** until an improvement in patient status is noted.

N.B. These **3 steps** *(**position**, **adrenaline** and **oxygen**)* are the only steps during the life- threatening phase of anaphylactic shock.

4- **Hydrocortisone** sodium succinate 200 mg **I.V.**

5- **Anti-histaminics**.

6- **Call ambulance**.

2) Angioedema:

Definition: Rapid development of edematous swelling involving skin, subcutaneous & submucosal tissues in various body parts.

Clinical Features of angioedema:

- Rapidly developing **edema** appears in less than half an hour and may last several days.
- There is severe **edema** of the face, lips, circumoral tissues, around the eyes, chin, tongue and also may affect the parotid.
- This swelling appears smooth, diffuse, painless with no change in temperature of the affected part, often there is pruritus.
- **Swelling** of the **nasopharynx** and **larynx** may produce **respiratory emergency**.

Types & Etiology of Angioedema:

(1) **Hereditary angioedema:** a **complement** mediated angioedema which is a rare autosomal dominant trait, there are **two** types:

a. Type **one** HAE: **low** level of C1 esterase inhibitor protein of the plasma complement system (**quantitative** deficiency). It represents 85% of cases.

b. Type **two** HAE: Small number of cases are characterized by normal or even increased level of **non-functional** C1 esterase inhibitor protein (**qualitative** deficiency), it represents 15% of cases.

Precipitated by: Blunt injury, trauma of dental procedures and emotional stress. Also, may be precipitated by injection of drugs.

Affected individuals are highly susceptible to laryngeal edema causing respiratory obstruction & death. (demonstrates disease rarity)

☑ **Management of HAE**: The concept is to **supply** the patient with C1 esterase inhibitor or **raise** its level.

1- Plasma infusions (fresh frozen plasma) help in replacing the missing C1 esterase inhibitor activity.

2- Synthetic androgen "stanozolol": **2.5 – 10 mg daily**.
↪ should be avoided in liver disease since it causes cholestasis (stoppage or suppression of bile flow).

3- Plasmin inhibitors: aminocaproic acid & its analogue tranexamic acid (can inhibit kinin system) are useful preoperatively.

4- Avoid any precipitating factors.

(2) **IgE mediated angioedema**: (IgE dependent)

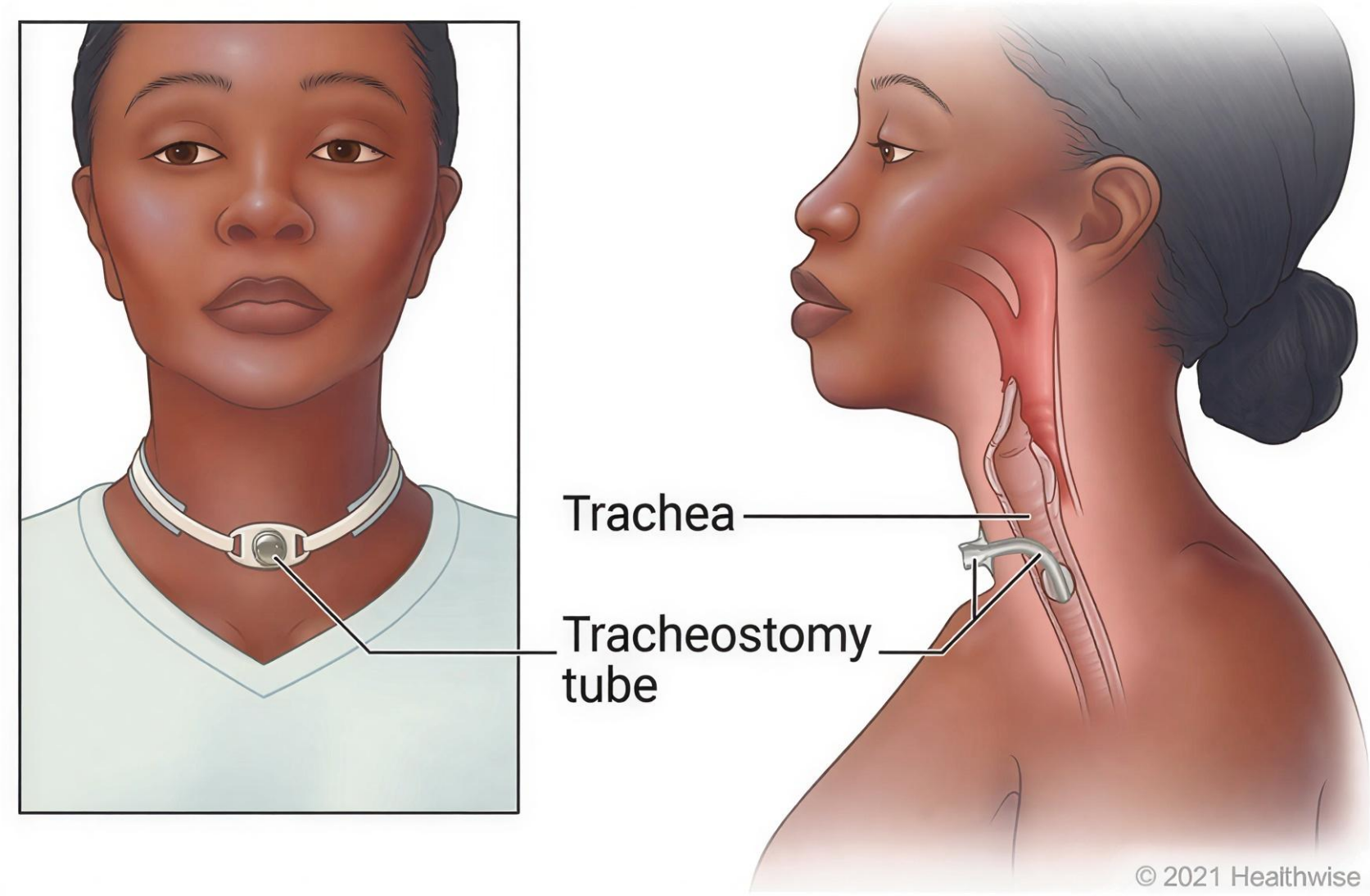
- ► They are associated with high levels of IgE and low IgA levels.
- ► They may represent atopic reactions with specific antigen sensitivity (drugs, foods, pollens).
- ► Frequently, it may be associated with urticaria.

(3) **Idiopathic non-IgE mediated angioedema**:

- ► Affect 5-10% of population.
- ► It is not characterized with abnormal IgE levels.
- ► It may be precipitated by direct mast cell releasing agents.
- ► This can be induced by trauma, and drugs as opiates, antibiotics, and contrast media.
- ► Drugs may directly affect mast cell, causing the release of chemical mediators.
- ► The reaction may also be the result of overdose, toxicity or side effects of the drugs.

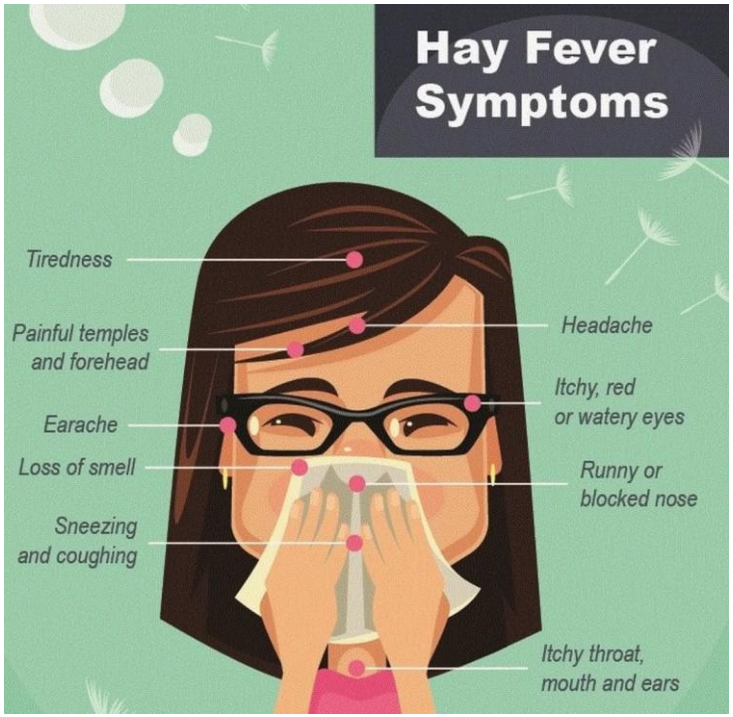
Treatment / Management of Angioedema:

1) Identification of the angioedema type and **removal** of the **cause** (may be difficult).
2) Immediate relief of **swelling** particularly if **larynx** is involved, by **I.M.** or **S.C.** injection of **0.5** – **1.0 ml** of (**1/1000**) **adrenaline**.
3) Less severe attacks can be managed by I.M. injection of **anti-histaminics**.
4) **Corticosteroid** in severe cases.
5) If this fails emergency **tracheotomy** may be life-saving.



3) Hay Fever (Allergic Rhinitis)

- **Definition:** Recurrent (seasonal) form of allergy to wind born pollen grains, certain food or dust.
- It is seasonal, i.e. common in spring and early summer.
- **Mechanism:**
  It is due to antigen-antibody (IgE) reaction on the surface of mast cells with the release of histamine and other mediators in mucous membrane of upper respiratory tract and conjunctiva.



Clinical Features of Hay Fever:

- Itching in the nose and profuse watery nasal discharge.
- Paroxysms of sneezing and coughing.
- Conjunctival irritation and lacrimation.
- **Headache** and depression.

Treatment / Management of Hay fever:

1. **Antihistaminic**.
2. **Steroid** in refractory cases.
3. **Desensitization**: antigen is administered on weekly basis at low dose several weeks before pollen season.
4. **Avoid** contact with the causative pollen.

TREATMENT FOR ALLERGY HEADACHES

Antihistamines

They block the effects of the chemical histamine, which is responsible for sneezing, itchy eyes, and runny nose, commonly associated with allergies.

Decongestants

They can be either oral or nasal and are the best option for treating nasal congestion that leads to headaches. They relieve the stuffiness and pressure in the sinuses, easing the pressure in your head.

Intranasal Corticosteroids

They work well for allergic rhinitis and help reduce your nasal congestion and runny nose.

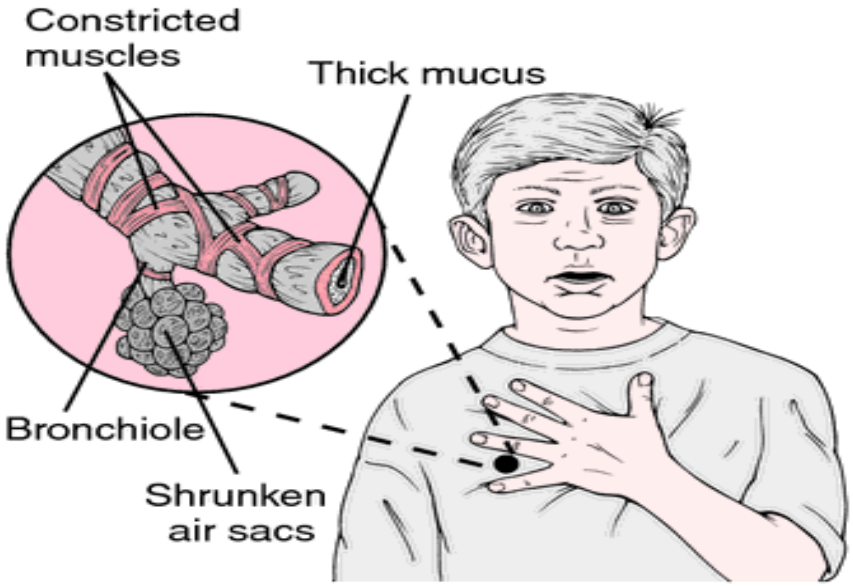
4) Bronchial Asthma

Definition: It is an allergic disease characterized by recurrent attacks of acute breathlessness.

Mechanism:

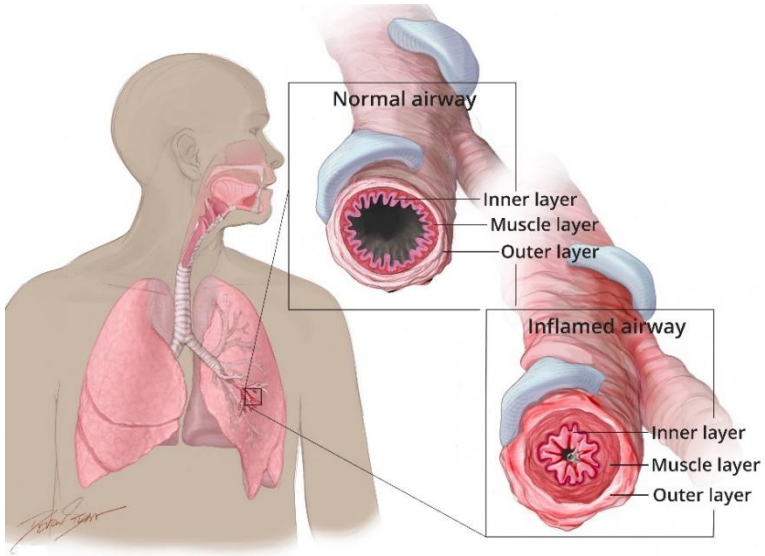
The patient is abnormally *sensitive to various substances inhaled or ingested,* allergic reaction results in *release of* ***leukotrienes*** slow-reacting substance of anaphylaxis (***SRS-A***) which is the **main mediator** in bronchial asthma, resulting in:

- Spasm of the smooth muscles of the bronchi.
- Swelling of the bronchial mucosa.
- Exudate of mucous.



Clinical Features of Asthma:

- **Short forceful inspiration** aided by accessory muscles of respiration.
- Long easily heard **wheezing** expiration.
- Expiration is **not** capable of deflating the chest.
- Face is pale, nose, lip and ear are **cyanotic**.
- The attack may last from half an hour to several hours.
- Very prolonged attack is called status asthmaticus.



Symptoms	Physical findings
• Shortness of breath	• Rapid, shallow respirations
•Wheezing	• Rapid pulse
• Difficult breathing	• Pallor or cyanosis
• Cough	• Diminished breath sounds
• Anxiety	• Generalized retractions
	• Frequent pausing to catch the breath when talking
	• Hyperexpansion of the chest

Emergency Management / Treatment of Asthma:

1. Stop dental procedure.
2. Check that airway is clear.
3. Loosen tight cloths.
4. Permit the patient to sit upright.
5. Ensure that the room is airy and cool.
6. The patient may carry self-medication as:
   - ❖ Aerosol containing isoprenaline or adrenaline.
   - ❖ Sublingual tablets of isoprenaline.
7. **I.M.** or **S.C.** injection of **0.5 ml** of (**1/1000**) **adrenaline**.

In case of Status Asthmaticus

- ✓ Hospitalization.
- ✓ Oxygen inhalation.
- ✓ Corticosteroids.
- ✓ I.V. aminophylline.

***NOTES*:**

- In **less** severe cases the need of sedatives, e.g., diazepam may be used.
- Sedation: the use of sedative drugs in **severe** or **prolonged** asthmatic attacks are absolutely contraindicated because they depress the central nervous and depress the respiratory systems.
- Anti-histaminics are of no value, where **Leukotrienes** are the important mediators of reaction not histamine.
- Anti-histaminics are slowly acting so they are of no value in emergency.

5) Urticaria (Hives)

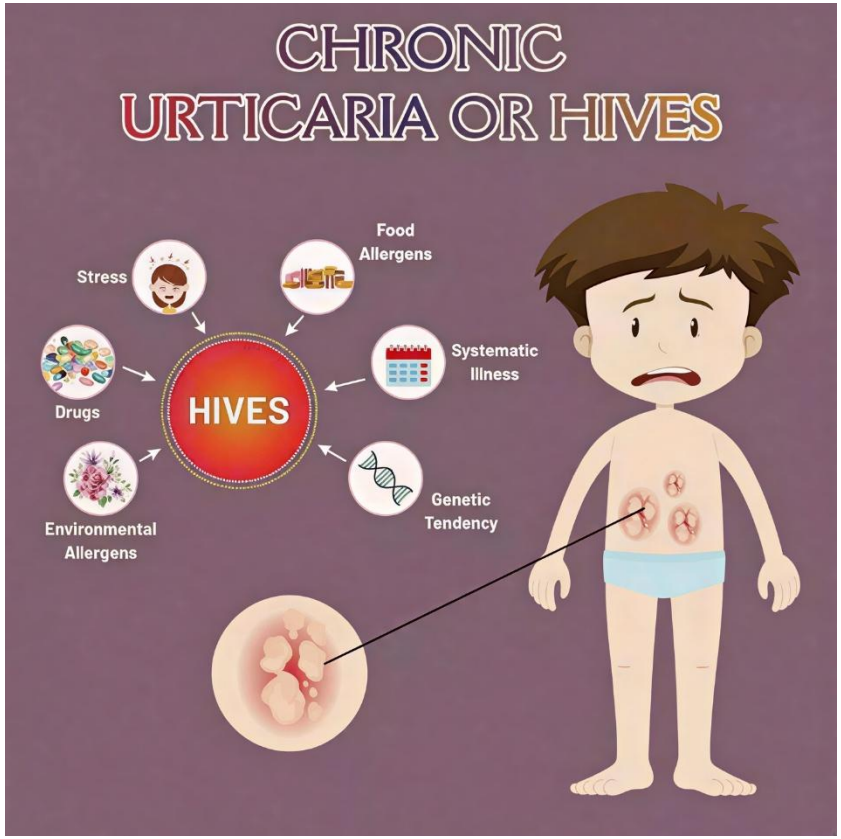
Definition: Common allergic reaction on skin varying from small localized papules to extensive large coalescing plaque which is erythematous and characterized by **itching**.

Mechanism:

This type of allergy is due to drugs, food or certain bacteria that react with IgE on mast cells resulting in the release of histamine and other mediators acting on **superficial vasculature**.

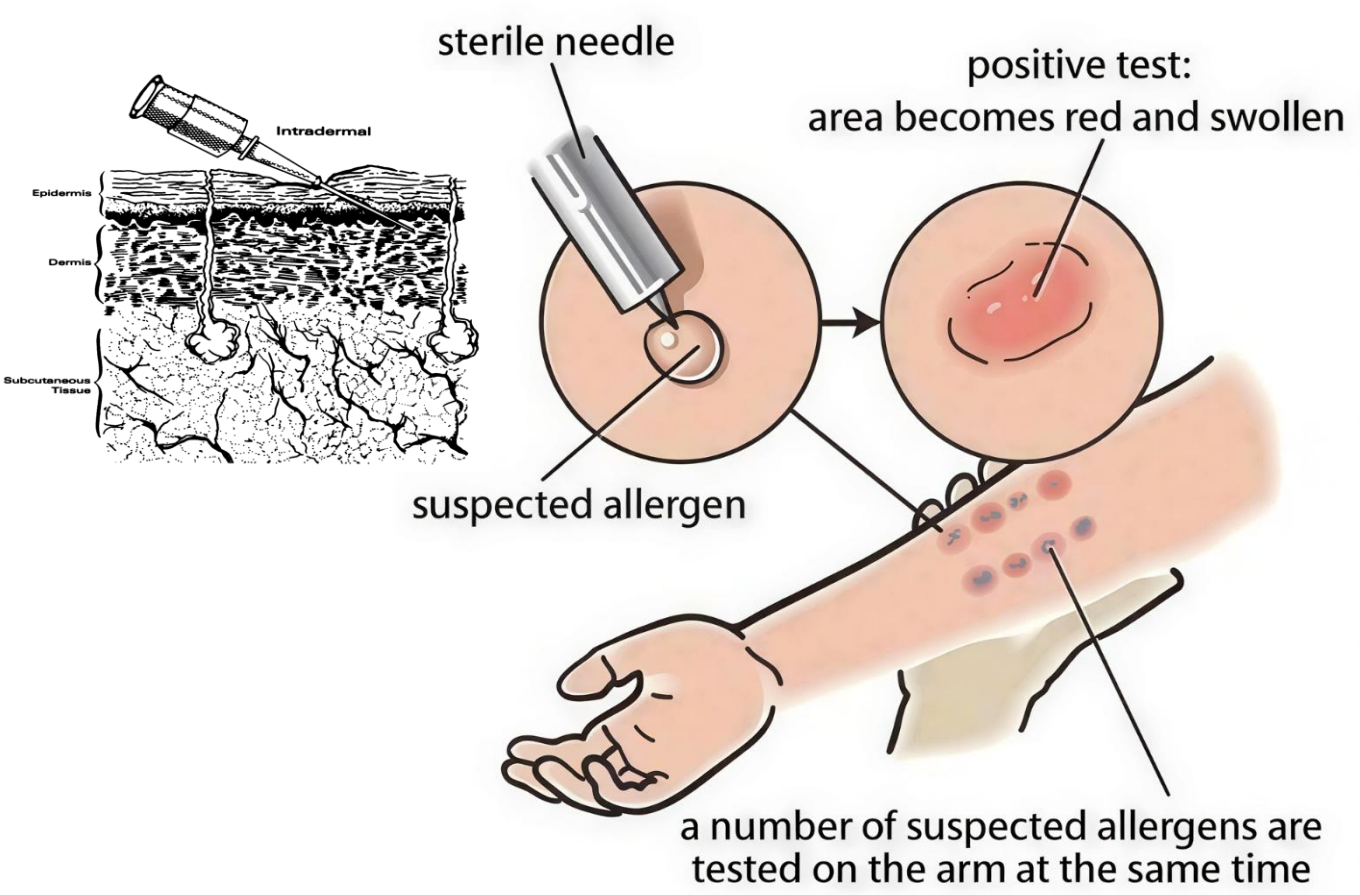
Management / Treatment of Urticaria:

- ✓ Removal of the causative factor: management of septic foci, since chronic urticaria may be related to septic focus.
- ✓ Anti-histaminics.
- ✓ Corticosteroids.



Local Anesthetic Allergy Testing (Intradermal Test)

1. The local anesthetic to be tested must be **free of** all **additives**, **preservative** and **vasoconstrictor**.
2. **Prepare 1 : 10 dilution** by drawing **0.1 mL** of the **full-strength** anesthetic solution into a syringe, placing it into a sterile vial, and then **diluting** with **0.9 mL** of **sterile saline** (**0.9 % sodium chloride**).
3. **Prepare 1 : 100 dilution** by drawing **0.1 mL** of the **1 : 10 diluted** anesthetic solution into a syringe, placing it into a sterile vial, and then **diluting** with **0.9 mL** of **sterile saline** (**0.9 % sodium chloride**).
4. Sterile **1-mL** tuberculin **syringes** with a **25**- or **27-gauge** needle are filled with each test dilution.
5. **Prepare** additional **syringes** containing the **anesthetic solutions** at **full** dental cartridge **strength** and a **control solution** of **sterile saline** (**0.9 % sodium chloride**).
6. Specific **injection areas** (usually on the **forearms**) are marked approximately **3 cm apart** and **prepared** by **cleansing** with a sterile alcohol swab and allowed to dry.
7. The **intradermal** (intracutaneous) **injection** is performed by inserting the needle tip, bevel up, **just underneath the surface** of the skin and injecting **0.1 mL** of the **agent**.
8. **First** administer the **1 : 100 dilution**, **then** the **1 : 10** dilution, **finally** the full-strength with 10-minute intervals between injections.
9. **Evaluate** each **injection site** for **15 – 20 minutes** for **erythema** or **wheal formation**.
10. If **no response** to the skin testing occurs, an intraoral injection may be given to **confirm** the result with the selected local anesthetic.



NOTES:

- In case you have a patient, who is **allergic** to ester- type of local anesthetics (LA), you have to switch to the amide-type.

- In rare cases if the patient is **allergic** to both ester and amide types of LA, inject your patient with **1%** of diphenhydramine solution which is an antihistaminic with weak local anesthetic effect or use general anesthesia.

Stomatitis medicamentosa (Allergic stomatitis)

- **Definition**: Eruptive lesions of the oral mucosa resulting from systemic administration of allergen (drugs or food).

- **Mechanism**:
  - Allergic stomatitis is mediated by **humoral antibodies**.
  - It may be attributed to **type I** (*less common*) or **type III** (*more common*) **hypersensitivity reaction**.
  - The allergen is administrated via injection, ingestion or percutaneous (absorption through skin).

- **Oral manifestation**:
  - The allergic manifestation is eruptive lesions which may occur in the mouth alone or skin alone or may involve both.
  - Acute multiple vesicles and ulcers similar to **erythema** multiforme.
  - Angioedema of lip and oral mucosa.
  - Urticaria of lip.
  - The oral manifestation is **less** common than that the cutaneous lesion (Dermatitis medicamentosa).

Type IV Hypersensitivity Reaction (Contact Allergy)
Stomatitis Venenata / Dermatitis Venenata

- **Definition**: It is a **delayed** allergic reaction of skin or oral mucosa to local **contact** with foreign substance (allergen).

- **Basis of reaction** (**Mechanism**):
  - Allergic contact stomatitis is mediated by **cell-mediated immunity** (**TH1** & **Tc**).
  - The Langerhans cells, mucosal macrophages, play a major role in recognition, processing and presentation of antigen to T-cells.
  - Sensitization on primary contact takes several days, but once occur it lasts for years/life because of **memory cells** development.
  - Second contact leads to release of sensitized T-cells which are able to proliferate and release **lymphokines**.
  - **Lymphokines** produce tissue damage via:
    1- **Tumor necrosis factor Beta** (**TNF-β**) which is **lymphotoxin**: **non- specifically** kills some cells.
    2- **Chemotactic factor**: **attract** macrophages which further secrete various kinds of mono-kines aiding in tissue damage.

Clinical Features of Type IV Hypersensitivity:

- **Stomatitis venenata** (**Contact stomatitis**): The oral reaction may be mild or severe and usually localized in the form of:
  - Burning and itching at the site of contact followed by erythema, edema, vesicles or ulcers.
  - Localized atrophy of tongue coating.
  - Cheilitis (dryness, scaling of lip).
  - Angular cheilitis.

- **Dermatitis venenata** (**Contact dermatitis**):
  - Perioral skin may show itching, burning, erythema, vesicles or urticarial rashes.
  - Dentist's or technician's fingers may also be affected when handling dental materials.

Diagnosis of **contact allergy (type IV)**:

1- History of contact with allergen.

2- Clinical examination: erythema, edema, vesicle & ulceration.

3- Positive patch test.

Patch test: for **allergens** (e.g. scrapping of denture):

a) **Dermal test**: Application of allergen to the skin:

1) Allergen is applied to the skin with moist gauze on one arm and control moist gauze alone on the other.
2) Allergic individuals show wheel reaction within 24-72 hours at the site of contact with allergen.

b) **Epimucous test**: Application of allergen to oral mucosa via:

1) Rubber suction cup applied to cheek mucosa.
2) Incorporation into orabase in mucobuccal fold.
3) Incorporation into oral adhesive spray.
4) Placing it on palatal aspect of denture.
5) Covering all palatal surface of denture with tin foil except small area to test sensitivity.

Treatment of **contact allergy (type IV)**:

☺ Elimination of the causative agents.

☺ Antiseptic agent to minimize secondary infection.

☺ Topical anesthetic to relief pain.

☺ Anti-histaminics.

☺ Steroid (*topical or systemic).*

- **Fixed drug eruption**: an example of type IV hypersensitivity reactions:
  - The eruptions (lesions) appear at the **exact same site** whenever the drug is taken.
  - The **drug** is **conjugated** with the body **protein** in the vascular bed supplying a particular area.
  - The **tongue** is a common site for fixed drug eruption.